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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,682	03/17/2004	Akira Asakura	13735 US1 (C038435/010970	9826

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

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01/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/802,682	ASAKURA ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 9, 20-22, 25 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,20-22, 25 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The examiner acknowledges the Amendment filed Sept 27, 2007. Claims 1, 2, 30 and 31 have been amended; the amendment has been entered. Claims 4-8, 10-19, 23-24 and 26-27 were previously canceled. Claims 1-3, 9, 20-22, 25 and 28-31 are pending and under examination.

Detailed Action

Rejection made in the Office action of March 27, 2007 (previous action) and not repeated below are withdrawn due to amendment.

35 U.S.C. 112 first paragraph

Scope of enablement

Claims 1-3, 20-22, 25, 28, 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the alcohol and aldehyde dehydrogense of SEQ ID NO: 5, 6, 7, and 8, does not reasonably provide enablement for any amino acid sequence comprising a sequence that has at least 90% identity to SEQ ID NO: 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Having 90% identity, i.e. having 58 random mutations in the protein of 579 amino acids, imposes on a skilled artisan an extremely lengthy experimentation that is undue. Guo et al. 2004 (Protein tolerance to random amino acid change, PNAS, 101/25, 9205-9210, enclosed) teach that the fraction of random single substitution

mutations which inactivate a protein of about 300 amino acid (human 3-methyladenine DNA glycosylase) is 0.34 and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 and formula 1) on page 9206 left column, that the fraction of active mutants for multiple mutations may be raughly estimated by formula $(1\text{-}0.34)^n$ where n is the number of mutations introduced. Applying this estimate to the instant protein having 90% identity, i.e., 58 mutations of SEQ ID NO: 8 or SEQ ID NO: 5, gives only $(.66)^{58}$ i.e., 3.42×10^{-12} of random mutants being active. At 95% identity $(.66)^{29}$, i.e., 5.87×10^{-7} would be active. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within about a million inactive mutants as is the case for the claims limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish, but finding a few mutants within hundreds of billions (exactly 2.9×10^{11} in the case at hand) as in the claims to 90% or less identity would not be possible without undue experimentation, especially that the presented calculation relates to viable mutants only. These viable mutants have to be further screened for having aldehyde dehydrogenase activity. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. It is noted that not only is the quantity of experimentation overwhelming in the instant situation but the specification provides no guidance with regard to what variants to make in order to

reduce the amount of experimentation to a reasonable level. Applicants do not teach in details how to modify SEQ ID NO: 8 so that the modified protein, having 58 mutations was still having the same enzymatic activity as the parental one.

In summary, the claims are rejected.

In addition, claim 2 and 3 are specificaly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the plasmid comprising genes encoding SEQ ID NO: 5 and SEQ ID NO: 8 (plasmids pSSAB201 and pSSBA201), does not reasonably provide enablement for an enzyme that comprises a combination of at least two amino acids sequences each of said sequences being selected from the group of SEQ ID NO: 8 and SEQ ID NO: 5 and amino acid sequences that are at least 90% identical to SEQ ID NO:8 or SEQ ID NO: 5. The reasons for this rejection were explained in the previous actions. The main conclusion has been: without a further guidance on the part of Applicants related to the structure of chimeric enzymes, one skilled in the art is forced to construct numerous combination of disclosed sequences or sequences that are at least 90% homologous to them, express the chimeric proteins, examine the enzymatic activity of the expressed constructs with a low probability of success. Thus the experimentation left to those in the art is undue.

In summary, the claims are rejected.

Response to Applicants' arguments

1. In their current REMARKS page 9, line 1 Applicants emphasize that the specification (page 34, line 20 to page 35, line 4) discloses that the nearest

homologues of Enzyme B (SEQ ID NO: 8) exhibit a maximum homology of 26-31% with known enzymes.

Applicant's argument has been fully considered but is found not persuasive, because the claims are rejected for lack of support for their full scope and not over prior art.

2. Applicants also turn the examiner's attention to Table 7 presenting homologies of amino acids sequences of four disclosed enzymes. The homologies are from 83 to 89 percent. Applicants' position is, "Applicants enabled the full scope of the amended claims by unambiguously identifying enzymes having highly homologous polypeptide sequences and sharing a common function—AADH"; see the table on page 9 and the text in the first line of page 10.

Applicants' position has been fully considered but is found not persuasive. Providing enzymes of SEQ ID NOs: 5, 6, 7 and 8 whose homologies are presented in Table 7 is **not a sufficient guidance** for the structure of any variant of SEQ ID NO: 5 or 8 having 90% identity and required function. In addition the data in Table 7 do **not provide any guidance** as to the structure of a chimeric protein claimed in claims 2 and 3.

In conclusion, claims 1-3, 20-22, 25, 28, 30-31 re rejected.

Conclusion

Claim 9 is allowed for the reasons indicated by the examiner in the First Office Action on merits on Dec. 1, 2004. Claims 1-3, 20-22, 25, 28-31 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action: In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-1600. The fax phone number for this Group is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 872-9306.

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Malgorzata A. Walicka, Ph.D.
Patent Examiner